Remarks:

Claims 14-25, 27-30, and 42 remain for consideration in this application with claims 14, 19, 27, and 42 being in independent format. Claims 14, 19, 27, and 42 have been amended and claims 1-13 and 31-41 have been withdrawn pursuant to a restriction requirement. Claim 26 has been previously cancelled.

Independent claims 14, 19, 27, and 42 have been amended to recite "a compound of the formula $(CH_3)_3N^+(CH_2)_nCOO^-$, with n equal to 1" in lieu of the term "glycine betaine." This formula was previously recited in the claims as originally filed; however, it was subsequently deleted because once the claims were amended to limit "n" to 1, Applicant considered the structure redundant with the term "glycine betaine." However, in order to clarify for the Examiner the intended compounds, Applicant has reintroduced this structural formula into the claims.

As an initial matter, Applicant notes that the Office Action Summary sheet indicates that the Action is both Final and Non-final. Applicant's representative spoke with Examiner Betton on October 20, 2008, who clarified that the Action was intended to be Non-final. Applicant respectfully requests confirmation of this in the next communication.

Turning to the Office Action, Applicant notes with appreciation that the previous written description rejection and the rejections based upon U.S. Patent No. 6,287,765 and U.S. Pat. App. Pub. No. 2002/0034757, both to Cubicciotti et al. and U.S. Patent No. 6,399,785 to Murphy et al. (hereinafter "Murphy") have been withdrawn.

However, the Examiner has rejected claims 14-25, 27-30, and 42 as being obvious in view of the combined teachings of five references: U.S. Patent No. 4,605,548 to Ushiyama et al.

(hereinafter "Ushiyama"), U.S. Patent No. 5,405,614 to D'Angelo et al. (hereinafter "D'Angelo"), U.S. Patent No. 5,814,599 to Mitragotri et al. (hereinafter "Mitragotri"), U.S. Patent No. 4,911,916 to Cleary, and U.S. Patent No. 5,928,195 to Malamud et al. (hereinafter "Malamud"). Each of these references is newly cited in this Office Action, with the exception of Malamud, which was cited in the previous Office Action.

According to the Examiner, Ushiyama discloses a transdermal drug delivery system, while an electronically-based transdermal drug delivery is disclosed in D'Angelo. The Examiner concedes that neither Ushiyama nor D'Angelo teaches or suggests glycine betaine. The Examiner further states that D'Angelo "does not provide reasoning as to why it would be pharmaceutically advantageous to incorporate glycine betaine...into a transdermal drug delivery system." Office Action, page 7. However, the Examiner argues that the deficiencies of D'Angelo are resolved by the teachings of Mitragotri. Specifically, the Examiner asserts that although Mitragotri does *not* teach glycine betaine, it does teach that hydrophilic molecules have enhanced transdermal penetration (the Examiner then notes that based upon Applicant's specification glycine betaine is a hydrophilic compound). Next, the Examiner points to Cleary as teaching drug compatibility studies and states that based upon the combined teachings of Mitragotri and Cleary, it would be desirable to cover glycine betaine with a hydrophobic polymer for more effective transdermal administration. Importantly, at the top of page 8 of the Office action, the Examiner acknowledges that ***none of the above references teach "glycine betaine."*** However, the Examiner states that the teaching of "glycine betaine" comes from Malamud, which discloses a "betaine compound." The Examiner then asserts that the term betaine is interchangeable with the term glycine betaine (citing col. 5, line 38

of Malamud). Finally, at the end of the rejection, the Examiner argues that the effects observed with the mixtures in Malamud containing both glycine and betaine would be same as those observed with glycine betaine. Thus, the Examiner concludes that all of the claims are *prima facie* obvious in view of the combined teachings of these five references.

Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness in view of these references, and further that even if one had been established, Applicant has effectively rebutted a *prima facie* showing of obviousness with objective, empirical evidence. When claims are rejected as obvious in view of two or more references, a holding of obviousness must be based on "an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ___, 82 U.S.P.Q.2d 1385, 1396 (2007). That is, "either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (B.P.A.I. 1985). Mere conclusory statements cannot sustain an obviousness rejection as there must be "some *articulated reasoning* with some *rational underpinning* to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329 (Fed. Cir. 2006) (emphasis added) (*cited with approval in KSR*, 550 U.S. at ___, 82 U.S.P.Q.2d at 1396). Moreover, if the proposed modification or combination would render the prior art invention unsuitable for its intended purpose, or change its principle of operation, then there can be no suggestion or motivation to make such modification or combination. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

The present claims are directed towards controlled release pharmaceutical systems which include an effective amount of a compound selected from the group consisting of "a compound of the formula $(CH_3)_3N^+(CH_2)_nCOO^-$, with n equal to 1, pharmaceutically acceptable salts of said compound, and mixtures thereof." None of the cited prior art references teach or suggest a compound having the recited structure, pharmaceutically acceptable salts thereof, and mixtures thereof, as claimed. That is, the Examiner has already acknowledged that there is no teaching of "glycine betaine" in Ushiyama, D'Angelo, Mitragotri, or Cleary. Rather, the Examiner relies solely on Malamud for the teaching of the glycine betaine. However, as explained in detail below, Malamud discloses only an "alkyl-*N*-betaine surfactant" or "alkyl dimethyl glycine" (col. 5, ll. 38; 45), neither of which teach or suggest the claimed compound.

In the previous response, Applicant submitted a Declaration under 37 C.F.R. § 1.132 by Dr. Christian Grandfils, Ph.D., Assistant Professor at the University of Liège in Belgium. As explained in the Declaration, Dr. Grandfils has a Ph.D. in Biomedical and Experimental Sciences from the University of Liège, Belgium, and is currently an Assistant Professor and a member of the medicine faculty at the University of Liège. He is also the Director of the Interfacultary Center for Biomaterials (CEIB) at the University, and has spent the past 30 years researching tissue engineering, drug delivery systems, optimization of diagnostic systems, and *in vitro* biocompatibility testing of biomaterials. Thus, Dr. Grandfils is clearly an expert in this field.

In the Declaration, Dr. Grandfils explained the structural, chemical, and physio-chemical differences between the alkyl-*N*-betaine compounds disclosed in Malamud and the claimed compound. He further attested that because of these differences, a person of ordinary skill in the art

would not have found the claimed compounds to be obvious or predictable based upon the teachings of Malamud.

In more detail, Dr. Grandfils explained that Malamud is directed towards the delivery of microbicidal drugs comprising surfactants with spermicidal, antiviral, antibacterial, and antifungal activities, such as alkyl-*N*-betaine surfactants, in combination with an oxide. According to Dr. Grandfils, the drug's activity is centered on the association of the surfactant with the oxide to form a stable micellar structure in the compound. Dr. Grandfils explained in detail that the differences in structure between the disclosed alkyl-*N*-betaine and the claimed compound give rise to *fundamentally different and disparate physical and chemical properties*, which are neither predictable nor obvious in view of each other. For example, alkyl-*N*-betaine surfactants contain an alkyl chain, which Dr. Grandfils explained is responsible for generating the surfactant properties with the associated spermicidal, antiviral, antibacterial, and antifungal activities (i.e., the alkyl chain disrupts the cell membrane function of the microorganisms). This assessment was supported by Exhibit B, which was submitted with the Declaration (Birnie et al., *Antimicrobial Evaluation of N-Alkyl Betaines and N-Alkyl-N,N,-Dimethylamine Oxides with Variations in Chain Length*, 44 ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2514-2517 (Sept. 2000)). In contrast, as noted by Dr. Grandfils in the Declaration, the claimed compound *does not* exhibit microbicidal properties. Rather, it actually provides a *favorable* environment for microorganisms: (1) it has protective effects on spermatozoa; (2) it favors bacterial growth, and bacteria avidly uptake glycine betaine to protect themselves; and (3) it favors fungal growth and the development of yeast. Applicant supported these assertions with previously submitted reference materials (Exhibits E-K).

Therefore, based upon the structural and chemical differences between the claimed compound and the disclosed surfactants, Dr. Grandfils declared that a person skilled in the art would have *no reasonable expectation* that the alkyl-*N*-betaine surfactants disclosed in Malamud would be capable of generating the therapeutic properties of the claimed compound to treat thrombosis.

In summary, Applicant has already established, through objective evidence and information, that the claimed compound and the surfactants disclosed in Malamud have different chemical structures, which give rise to fundamentally different chemical and physical properties. Applicant respectfully asserts that the Examiner has improperly ignored the evidence and Declaration by Dr. Grandfils regarding Malamud and the differences between the claimed compound and the surfactants disclosed in Malamud. Moreover, the Examiner makes numerous unsupported assertions in the present Office Action, which contradict the evidence submitted by Applicant. Applicant respectfully submits that this is improper.

For example, despite Dr. Grandfils' Declaration, the Examiner continues to assert that the compounds disclosed in Malamud (i.e., mixtures containing glycine and betaine) would be expected to provide the same therapeutic effects as the claimed compound. Office Action, page 9. However, it is well know that a "presumption of obviousness based on a reference [allegedly] disclosing structurally similar compounds may be overcome where there is evidence showing there is no reasonable expectation of similar properties in structurally similar compounds." M.P.E.P. § 2144.09 (citing *In re May*, 574 F.2d 1082, 197 U.S.P.Q. 601 (C.C.P.A. 1978)). As reiterated above, in the previous response, Applicant effectively established that there would be no reasonable expectation of similar properties between the claimed compounds and the surfactants in Malamud. That is,

Applicant has demonstrated that not only would there be no reasonable expectation of similar properties, but in fact, the claimed compound and the surfactants in Malamud *do not* have similar properties (i.e., one is microbicidal, one is not). Although the Examiner believes one *might expect* the claimed compound and the compounds of Malamud to possess similar properties, Applicant effectively rebutted this presumption by showing that the compounds of Malamud do not have similar properties to the claimed compound.

In addition, when an Applicant has submitted evidence to rebut an allegation of obviousness, the Examiner *must* consider this evidence. M.P.E.P. § 716.01(a). "Where the evidence is insufficient to overcome the rejection, the examiner *must specifically* explain why the evidence is insufficient." M.P.E.P. § 2145. That is, if the submitted evidence is deemed insufficient, the Examiner should "specifically set forth facts and reasoning that justify this conclusion" and should avoid giving the evidence no weight, except in rare circumstances. *Id.*

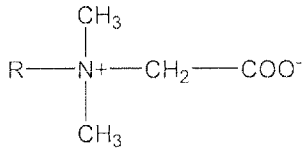
Applicant respectfully submits that this has not been done in the present case. Rather, instead of reconsidering the reliance on Malamud in view of the evidence submitted by Applicant, or responding with evidence of his own, the Examiner simply dismissed the Declaration as not being persuasive. The Examiner provided no substantive response to Applicant's arguments or to the evidence presented in the Declaration, while continuing to rely on Malamud as a basis for rejecting the claims. The Examiner indicated in the Office Action that the Declaration of Dr. Grandfils was "acknowledged and made of record." Office Action, page 2. The Examiner then set forth a brief summary of his interpretation of Applicant's arguments and the Declaration. Finally, the Examiner stated that "Applicant's arguments are considered but are not found persuasive." No other discussion

or explanation was provided for why the evidence presented in the response or Declaration was not persuasive. This is improper. *See* M.P.E.P. § 2145.

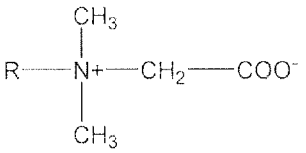
Further, it is unclear whether the Examiner actually considered the substance of the Declaration (in addition to acknowledging and recording it). For example, the Examiner stated that the "Declaration discloses that references Malamud and Murphy teach non-analogous art..." Office Action, page 2. However, Applicant respectfully submits that this is inaccurate, as there was no discussion of "non-analogous art" in the Declaration. That is, an assertion of "non-analogous art" is a legal argument, which was presented by Applicant in the remarks of the previous response. However, the Declaration by Dr. Grandfils was limited to scientific evidence and the technical knowledge of those skilled in the art pertaining to the known chemical and physio-chemical properties of the claimed compound, as compared to the compounds disclosed in the cited references. Accordingly, Applicant respectfully requests that the Examiner give meaningful consideration to the previously submitted evidence. Moreover, if such evidence is still not considered to be persuasive, Applicant respectfully requests that the Examiner provide a specific explanation in support of this conclusion.

As established above, there is no teaching or suggestion in Malamud of the claimed compound. Applicant further submits that one of ordinary skill in the art would have no motivation to modify Malamud to use the claimed compound. That is, Malamud is concerned with intravaginal delivery of microbicides comprised of an alkyl-*N*-betaine surfactant and an oxide. Malamud incorporates by reference three patents (U.S. Pat. Nos. 4,107,328, 4,839,158 and 5,314,917), which describe the preferred drugs for use in the device. Col. 5, ll. 34-43. The Examiner's attention to

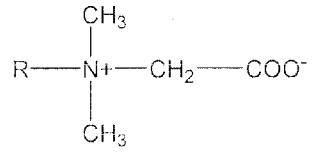
drawn to the attached Declaration signed by Jallal Messadek, the inventor named in the present application. Mr. Messadek has reviewed the patents cited by Malamud, which are discussed in the Declaration. In summary, *none* of the cited patents discloses the claimed compound. In particular, as Mr. Messadek explains in the Declaration, U.S. Patent No. 4,107,328 teaches as follows:

> "In general, a first component, namely, alkyl-N-betaine surfactant employed as a non-ionizing zwitterion can be written as:
>
> 
>
> Where R is a higher alkyl having from ***10 to 18 carbon atoms***. Illustrative of such alkyl-N-betaine is coco-N-betaine, cetyl-N-betaine, stearyl-N-betaine, isostearyl-35 N-betaine, or oleyl-N-betaine, or mixtures of the same."

Column 2, lines 23-36. U.S. Patent No. 4,839,158 discloses an "alkyl-*N*-betaine" having the structure



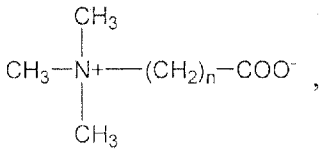
"where R is a higher alkyl group having from ***10 to 18 carbon atoms***." Col. 2, lines 14-49. Likewise, U.S. Patent No. 5,314,917 discloses an "alkyl-*N*-betaine" having the structure



"where R is a higher alkyl group having from ***10 to 18 carbon atoms, preferably from 12-16 carbon atoms***." Col. 4, line 48 – col. 5, line 18.

The mechanism of antimicrobial alkyl-*N*-betaine surfactants rests on their ability to disturb the microorganism's membrane phospholipids. This activity is *only* seen in alkyl-*N*-betaine

surfactants having long alkyl chains, as those described in the patents disclosed in Malamud above. In contrast, the presently claimed structure (below) would not have this functionality.



, where n equals 1.

Indeed, the claimed compound actually *favors* microbial activity, as explained in the Declarations. Thus, it cannot be said that the "alkyl-*N*-betaine surfactant" disclosed in Malamud would teach or suggest to one of ordinary skill in the art to use the claimed compound because these are different compounds, with different structures, and different functionalities.

Importantly, it is noted that Malamud never discloses "betaine" alone. Rather, as Mr. Messadek points out in the attached Declaration, the term is always disclosed as an "alkyl-*N*-betaine surfactant," which, contrary to the Examiner's assertions, is *not* interchangeable with "glycine betaine," or even "betaine." Applicant respectfully submits the Examiner is mis-characterizing the prior art in an attempt to make the disclosed compounds seem closer than they really are to the claimed compound of the recited formula, pharmaceutically acceptable salts thereof, and mixtures thereof.

As shown above, these are not the same or similar compounds. If the Examiner continues to rely on the disclosure of "alkyl-*N*-betaine surfactant" in Malamud as teaching or suggesting the claimed compound, it is respectfully requested that the Examiner provide scientifically-based reasoning and explanation to rebut Applicant's arguments. In particular, it is requested that the Examiner explain how one of ordinary skill in the art would have arrived at the claimed compound

from the particularly drawn structures for the "alkyl-N-betaine surfactants" disclosed expressly and by reference in Malamud, despite the known physical and chemical differences between these compounds. Simply dismissing Applicant's arguments as "not being persuasive" is insufficient to meet the Examiner's requisite burden when considering substantive evidence submitted by an Applicant. *See* M.P.E.P. § 2145.

Finally, the Examiner's attention is again directed to the previously submitted Declaration of Dr. Grandfils and Exhibit B (article by Birnie, et al., coauthored by Malamud). In the Declaration, Dr. Grandfils avers that there would be no scientific rationale to modify the surfactants disclosed in Malamud to remove the alkyl chain and replace it with a methyl group to arrive at the claimed compound structure. That is, removing the alkyl chain from the betaine surfactant in Malamud would defeat the spermicidal, antiviral, antibacterial, and antifungal activities of the surfactant and render the drug unsuitable for the intended microbicide purposes disclosed in Malamud. This is especially true in light of Birnie et al. above, which teach away from this modification by teaching that *longer* alkyl chains are preferred as they demonstrate better antimicrobial activity.

Specifically, on page 2515 under the Results section, Birnie et al. disclose that "Antimicrobial activity was very poor at lower chain lengths." The "lower chain lengths" referred to in Birnie et al. correspond to C_8 chain lengths, which were the shortest chain lengths even tested. Moreover, as shown in Table 2, higher chain lengths of C_{12}-C_{18} performed exponentially better. Thus, it cannot be said that one of ordinary skill in the art would have been motivated to replace the higher chain lengths in the alkyl-*N*-betaine surfactants disclosed in Malamud with the methyl group

of the claimed compound, as this would change the principle of operation of the microbicidal compounds used in Malamud (i.e., they would no longer be microbicidal).

This modification would also interfere with the surfactant's interaction with the oxide and inhibit the formation of the micellar structure necessary to create a stable microbicide compound. That is, as previously explained, the formation of the micellar structure is based upon the long alkyl chain on the surfactant, which would no longer be present to form the stable structure if the alkyl-*N*-betaine surfactant is replaced by the claimed compound. Thus, because the proposed modification would render the invention of Malamud unsuitable for its intended purpose, or change its principle of operation, there can be no suggestion or motivation to make such modification. *In re Gordon*, 733 F.2d at 902.

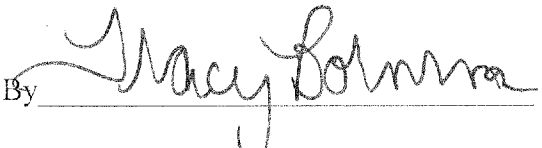
As Mr. Messadek summarizes in the attached Declaration, to arrive at the claimed compound, one of ordinary skill in the art would have had to ignore the state of the art regarding the use of alkyl-*N*-betaine surfactants according to the above formulas where R is a higher alkyl having from 10 to 18 carbon atoms, and ignore that such long alkyl chains are responsible for the microbicidal effects of the surfactant, as stated by Malamud himself, and clearly established by the published art (Exhibit B, page 2515, Discussion 2nd paragraph). One of ordinary skill in the art would have then had to select a compound below the cutoff for microbicidal efficacy as defined by Malamud and replace the higher alkyl chain having from 10 to 18 carbon atoms with a methyl group having only 1 carbon atom. Further, one of ordinary skill in the art would have to ignore that the resulting compound (glycine betaine) is known to *favor* bacterial and microbial growth and provides the ***opposite*** properties of those sought in Malamud. Finally, this information would have had to be combined

with four additional references to arrive (allegedly) at the claimed invention. Applicant respectfully submits that there would have been no such motivation for the many reasons already stated. Accordingly, Applicant respectfully submits that the claimed invention would not have been obvious to a person skilled in the art at the time of the invention, and independent claims 14, 19, 27, and 42 are therefore patentable over the art of record.

In addition, while dependent claims 15-18, 20-25, and 28-30 recite additional patentable features, these claims should also be in condition for allowance, as depending from patentable independent claims. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

In view of the foregoing, it is believed that no further issues exist with respect to this application. The Applicant respectfully requests a Notice of Allowance. Any additional fees due in conjunction with this amendment should be applied against our Deposit Account No. 19-0522.

Respectfully submitted,

By 

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